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Increased frequency of hypertension and coronary artery disease independent of age in primary hyperparathyroidism associated hypercalcaemia

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ABSTRACT

Aims: There are conflicting data in the literature regarding whether there is an increased frequency of coronary artery disease (CAD) in patients with primary hyperparathyroidism (PHP). In this study, we planned to investigate the frequency of CAD and hypertension (HT) in patients with PHP.

Methods: Patients with PHP aged 18 years and older who were admitted to the endocrinology clinic between September 2020 and February 2023 were included as the patient group, and age- and gender-matched individuals who presented with thyroid nodules between the same dates were included as the control group. A total of 217 patients, 114 with PHP and 103 as control group, were eligible for the study. The study was conducted as a retrospective data analysis and laboratory and demographic information of the patients and the control group were obtained from their files.

Results: Age and gender distribution of the patient group and the control group were similar (respectively; age: 55.6+12.9 years, 53.0+7.2 years, p=0.058, female/male distribution: 93/21, 80/23 p=0.48). The prevalence of HT and CAD was higher in the patient group (respectively; HT: 65.1%, 31.0%, p<0.001, CAD: 32.0%, 3.1%, p<0.001), while the prevalence of DM was similar (respectively; 18.1%, 17.3%, p=0.89). The prevalence of HT, CAD and DM was found to be the same among those with mild and severe PHP (respectively; HT: 65.6%, 64.4%, p=0.90, CAD: 38.3%, 23.3%, p=0.14, DM: 19.7%, 15.9%, p=0.62,). Age (β=0.10, odds ratio [OR];1.11 [95% confidence interval (95% CI);1.05-1.17], p<0.001) and calcium (β=0.67, OR;1.96 [95% CI;1.10-3.51], p=0.023) levels were found to be independent effective factors on CAD.

Conclusion: Increased calcium levels in PHP constitute an age-independent risk for CAD. In addition, elevated calcium increases the frequency of HT, which is a CAD risk factor.

Keywords: Primary hyperparathyroidism, hypertension, coronary artery disease, hypercalcaemia

INTRODUCTION

Primary hyperparathyroidism (PHP) is one of the most common endocrine hormone hypersecretions.[1] The diagnosis is made with the presence of normal or increased parathyroid hormone (PTH) levels despite increased plasma calcium (Ca) levels.[2] Increased laboratory use in daily practice has led to more frequent encounters with hypercalcaemia and PHP.[3] Since there is no known effective medical treatment for PHP, the only treatment is surgical resection of the abnormal parathyroid gland.[2] However, due to widespread laboratory use, a significant proportion of patients are detected at an asymptomatic stage that does not require surgery.[3] Indications for surgical operation in individuals with asymptomatic PHP are as follows: younger than 50 years of age, Ca levels increased by 1 unit in mg/dL compared to the upper limit of normal, increased urinary Ca (U Ca) level (400 mg/day), presence of osteoporosis or osteoporosis-related fracture, glomerular filtration rate <60 ml/min, kidney stones or nephrocalcinosis.[4]

Investigation of the relationship between increased PTH hormone levels and cardiovascular diseases and hypertension (HT) has a history of more than 30 years.[5] In the first studies, it was found that increased PTH levels in vitro increased aldosterone and cortisol secretion from adrenal cortex cells.[5] Later studies revealed that PTH-like peptide (PTHrp) structure has a similar effect.[6,7] The relationship between PTP and HT found in in vitro studies was also demonstrated clinically in the following years.[8,9] Improvement in HT and hyperaldesteronism in the postoperative period has been found in studies.[10,11]

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While there are studies in which no relation between PHP and CAD was found,[12] there are also studies in which a relation between PHP and CAD was found.[13] Despite the increased frequency of HT, the presence of HT in asymptomatic patients does not yet constitute an indication for operation in the guidelines.[4] The primary reason for this seems to be conflicting data on whether the frequency of cardiovascular disease increases in PHP.[10]

In this study, it was planned to investigate the relationship between PTH and Ca and the frequency of cardiovascular disease and HT in individuals with PHP.

METHODS

The study was carried out with the permission of Bursa City Hospital Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-5/12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted as a retrospective data review and individuals with PHP who were admitted to the endocrinology, diabetes and metabolic diseases clinic of University of Health Sciences Bursa City Hospital between September 2020 and February 2023 were included in the study.

Inclusion Criteria

18 years and over, diagnosed with PHP

Exclusion Criteria

Familial hypocalciuric hypocalcaemia, secondary and tertiary hyperparathyroidism, pregnant women, those receiving treatment for systemic diseases other than DM, HT and CAD.

Study Design and Work Plan

Plasma Ca, phosphorus (P), PTH, creatinine (Cr), glomerular filtration rate (GFR), vitamin D3 (VitD3), UCa, albumin, thyroid stimulant hormone (TSH), low density lipoprotein, information on age, height, weight, bone density measurement (dual-energy x-ray absorptiometry [DEXA]), medications, diabetes mellitus (DM), HT and CAD were obtained from patient files. Body mass index (BMI) was calculated as kilogram/m², corrected Ca (mg/dL) was measured as total serum Ca, corrected by 0.8 mg/dL for every 1 g/dL change in serum albumin concentration of the patient relative to 4.0 g/dL.

The diagnosis of PHP, differentiation between PHP and familial hypocalciuric hypercalcaemia, and differential diagnosis of normocalcaemic PHP and secondary hyperparathyroidism were made in accordance with the recommendations of the current guidelines.[4,14] According to the current guidelines, patients whose plasma Ca levels increase less than 1 mg/dL compared to the upper limit of normal are defined as mild PHP and those with an increase of 1 mg/dL and above are defined as severe PHP.[14]

The presence of CAD was considered as stent implantation after previous percutaneous catheterisation or hospitalisation due to acute myocardial infarction (aMI) and necessary information was obtained from patient files and recorded as CAD present/absent. Those with a current diagnosis of HT were checked whether they had been prescribed anti-HT medication in the last 3 months from the electronic prescription system, and HT status was recorded as present or absent.

Age and gender matched patients who were followed up for euthyroid thyroid nodule were selected as control group.

Statistical Analysis

After the normal distribution was determined by Kolmogorov-Smirnov test, an independent samples t-test was applied to data with a normal distribution. The Pearson's chi-squared test was used to compare ratios. Pearson and Spearman tests were used to determine the correlation between the data, Binary logistic regression analyses were used to determine whether the correlated data were independent factors. A p-value of less than 0.05 was considered statistically significant. IBM® Statistical Package for the Social Sciences (SPSS) statistics 20 was used to compare the data.

RESULTS

A total of 217 patients, 114 with PHP and 103 as control group, were eligible for the study. Both PHP and control group and mild and severe PHP groups were compatible with each other in terms of age, BMI and sex ratios (Table 1 and Table 2).

Table 1. General characteristics and laboratory properties of PHP and control group

	Control group (103)	PHP (114)	p
Age (year)	53.0+7.2	55.6+12.9	0.058
Female/male	80/23	93/21	0.48
BMI (kg/m²)	29.47	28.44	0.23
Creatinine (mg/dL)	0.74+0.20	0.78+0.26	0.17
Ca (mg/dL)	9.3+0.39	11.80+0.96	<0.001
P (mg/dL)	3.6+0.45	2.30+0.48	<0.001
PTH (ng/L)	34.5+16.0	227.1+158.9	<0.001
Vit D3 (ng/mL)	20.16+11.08	15.07+7.93	<0.001
TSH (uIU/mL)	3.06+10.30	1.61+1.09	0.17
LDL (mg/dL)	126.89+37.29	115.42+26.13	0.011
DEXA			
L1-4 (T score)	-	-1.85+1.61	
Femur total (T score)	-	-1.48+1.08	

BMI: Body mass index, Ca: Calcium, P:Phosphorus, PTH: Parathyroid hormone, Vit D3: Vitamin D3, TSH: Thyroid stimulant hormone, LDL: Low density lipoprotein, DEXA: Dual-energy x-ray absorptiometry, L1-4: lumbar spine 1-4.

Table 2. General characteristic and laboratory features of the mild and severe PHP group

	Mild PHP (53)	Severe PHP (61)	p
Age (year)	56.1+11.9	55.2+13.8	0.72
Female/male (n)	46/7	47/14	0.18
BMI (kg/m²)	28.51+5.58	28.37+4.37	0.91
Creatinine (mg/dL)	0.67+0.14	0.86+0.28	<0.001
Ca (mg/dL)	11.01+0.29	12.36+0.88	<0.001
P (mg/dL)	2.09+0.45	2.63+0.33	<0.001
PTH (ng/L)	156.2+68.0	277.1+184.3	<0.001
Urinary Ca (mg/day)	326.3+148.6	355.6+163.8	0.35
Vit D3 (ng/mL)	15.3+7.2	14.9+8.5	0.77
TSH (µIU/mL)	1.67+1.05	1.58+1.11	0.68
LDL (mg/dL)	116.78+25.34	114.27+26.94	0.61
DEXA			
L1-4 (T score)	-1.64+1.54	-2.02+1.67	0.26
Femur total (T score)	-1.32+1.21	-1.59+0.97	0.27

BMI: Body mass index, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone, Vit D3: Vitamin D3, TSH: Thyroid stimulant hormone, LDL: Low density lipoprotein, DEXA: Dual-energy x-ray absorptiometry, L1-4: lumbar spine 1-4.

Clinical Findings

The frequency of HT, CAD and kidney stones were higher in patients with PHP compared to the control group, on the other hand the frequency of DM was similar (Figure 1 and Figure 2).

The general characteristics and laboratory parameters of the study group with PHP and the control group are shown in Table 1. The frequency of HT (64.4%, 31%, p<0.001, respectively), CAD (23.3%, 3.1%, p<0.001, respectively) and kidney stones (26.2%, 3.1%, p<0.001, respectively) were higher in patients with mild PHP compared to the control group, whereas the frequency of DM was similar (15.9%, 17.3%, p=0.83, respectively).

Comparison of clinical and laboratory characteristics of patients with mild PHP and severe PHP is given in Table 2.

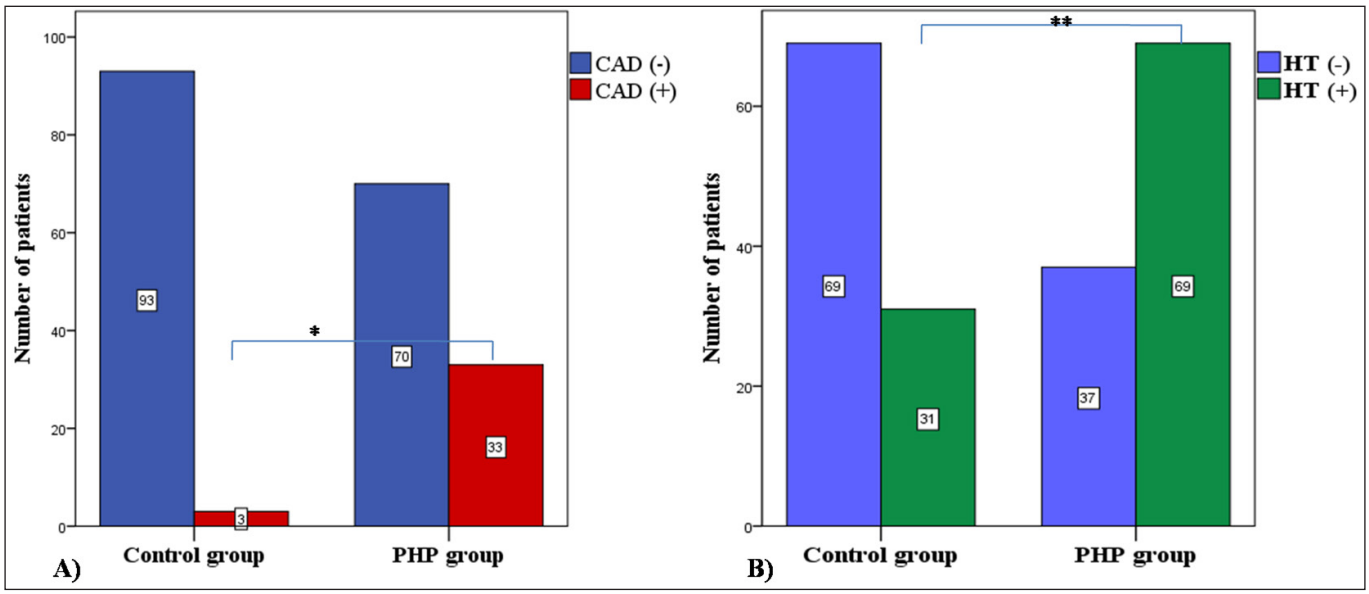

Figure 1. Prevalence of CAD (A) and HT (B) in the patient group and control group (*p<0.001, **p<0.001).

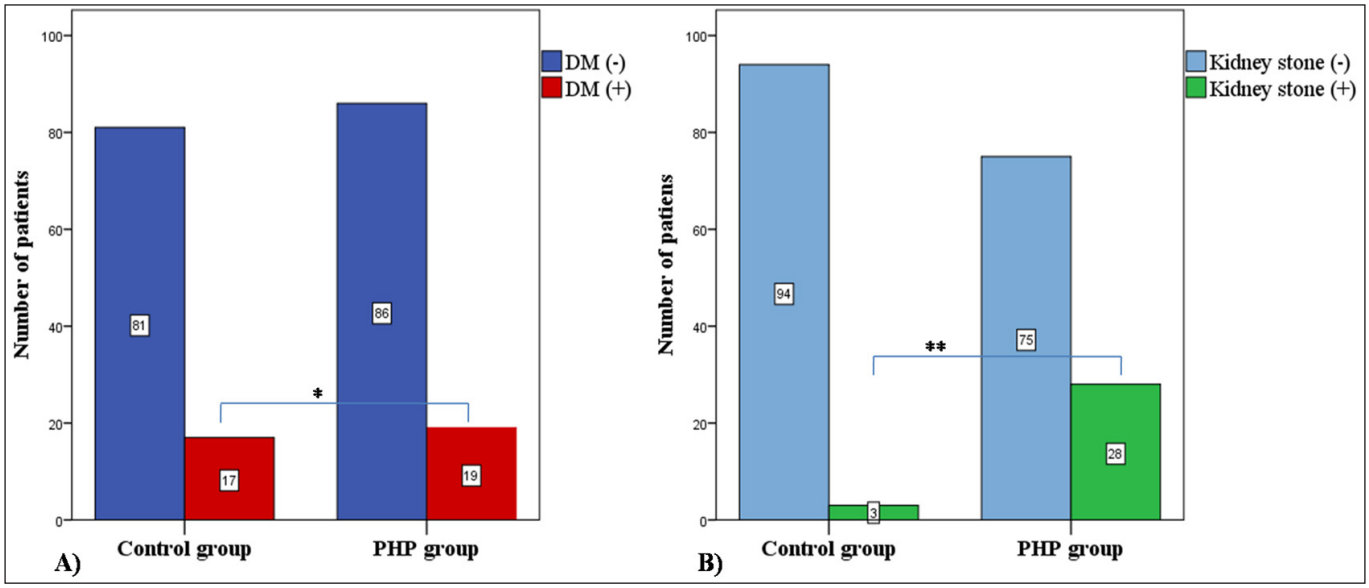

Figure 2. Frequency of DM (A) and kidney stone (B) in the patient group and control group (*p=0.89, **p<0.001).

Laboratory

The laboratory characteristics of the study and control groups are shown in Table 1.

While there was a difference between the Ca levels of those with CAD and those without CAD (11.6+1.2 mg/dL, 10.4+1.4 mg/dL, p<0.001, respectively), there was no difference between the PTH levels (249.7+142.7, 188.2+168.7, p=0.054, respectively).

When plasma Ca levels of patients with kidney stones were compared with plasma Ca levels of patients without kidney stones, it was observed that plasma Ca levels were higher in the group with kidney stones (11.9+1.3 mg/dL, 10.3+1.3 mg/dL, p<0.001), PTH levels (225.4+198.4 ng/L, 198.0+150.8 ng/L, p=0.50, respectively) and U Ca (337.11+138.21 mg/day, 342.24+169.17 mg/day, p=0.88, respectively) were similar between the two groups.

Plasma Ca levels of HT patients were higher than non-HT patients (11.1+1.5 mg/dL, 10.1+1.3 mg/dL, p<0.001, respectively), and PTH levels of HT and non-HT patients were not different (225.3+144.5 ng/L, 173.3+182.7 ng/L, p=0.10, respectively).

Correlation and Regression Analysis

A correlation was found between CAD with Ca and PTH levels (Table 3).

Table 3. Parameters that correlate with HT, DM and CAD

HT	DM	CAD
Age (r=0.42, p<0.001)	Age (r=0.21, p=0.002)	Age (r=0.39, p<0.001)
Gender (r=0.08, p=0.24)	Gender (r=0.08, p=0.27)	Gender (r= -0.06, p=0.42)
Ca (r=0.33, p<0.001)	Ca (r= -0.10, p=0.89)	Ca (r=0.42, p<0.001)
PTH (r=0.16, p=0.09)	PTH (r= -0.09, p=0.31)	PTH (r=0.17, p=0.07)
DM (r=0.33, p<0.001)	CAD (r=0.15, p=0.035)	DM (r=0.15, p=0.035)
CAD (r=0.47, p<0.001)	HT (r=0.33, p<0.001)	HT (r=0.47, p<0.001)

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, Ca: Calcium, PTH: Parathyroid hormone.

Logistic regression analysis showing the effect of independent variables on CAD is shown in Table 4. Age and Ca levels stand out as independent factors effective on CAD (Table 4).

DISCUSSION

Present study, it was found that the frequency of CAD and HT increased in PHP and hypercalcaemia was an effective factor on both the presence of CAD and HT. There was no association between PTH levels and HT and CAD.

One of the results obtained from our study was that the frequency of HT was higher in both mild and severe PHP. In present study, the prevalence of HT was found to be 31.0% in the control group and 65% in the PHP group and was compatible with the general literature.[15,16] In the study of Luigi[17] and colleagues (et al.), the prevalence of HT in PHP was found to be 81%, which was much higher than the general literature data.[16] The reason for this may be the small number of patients in the study of Luigi et al. Current guidelines[2,4] do not include HT among the indications for surgery in PHP. In the same guideline, it is stated that the results related with cardiovascular disease are not different between those with and without surgery and HT cannot be a reason for operation indication yet, due to reasons such as the persistence of HT in a significant proportion of operated patients.[2] PHP has been shown to cause increased activity in the renin aldosterone system both in vitro[5-7] and in clinical studies,[18] and improvement in the renin aldosterone system has been found after surgical treatment.[19] The approach regarding HT in PHP should not be all or none. In PHP, there is a study showing improvement in HT 6 months after surgery,[20] as well as a significant decrease in the frequency of HT and a decrease in the non-dipping pattern in the study by Luigi et al.[17] In another study, a decrease in both mean blood pressure and the number of drugs used was observed.[21] In the study by Beysel et al.[22] a decrease in systolic and diastolic blood pressure

Table 4. Independent variables affecting HT and CAD in logistic regression analysis

Dependent variable	Independent variable	β	Wald Chi-square	p	OR	OR (*95% C.I.)	
						Lower	Upper
	Constant	-14.48	14.16	<0.001	0.00		
Model 1	Age	0.10	13.93	<0.001	1.11	1.05	1.17
CAD	Ca	0.67	5.18	0.023	1.96	1.10	3.51
	PTH	0.001	0.10	0.76	1.01	0.99	1.04
	DM	0.73	1.41	0.24	2.07	0.62	6.87
	Gender	-0.66	1.06	0.30	0.52	0.15	1.82
	Constant	-13.25	12.79	0.00	0.000		
Model 2	Age	0.11	18.14	<0.001	1.12	1.06	1.18
HT	Gender	0.12	0.04	0.84	1.13	0.35	3.69
	Ca	0.61	4.63	0.03	1.85	1.06	3.22
	PTH	0.001	0.31	0.58	1.00	0.99	1.01
	DM	2.35	4.62	0.03	10.43	1.23	88.52

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, PTH: Parathyroid hormone, * 95% C.I.: Confidence interval.

was found postoperatively in both normocalcaemic and hypercalcaemic PHP patients, and improvement was also found in parameters considered as cardiovascular risk factors in the same study. One of the biggest problems here is whether the detected HT is essential HT or HT triggered by PHP. This distinction does not seem to be easy for now. Nevertheless, it may be more appropriate for the guidelines to reconsider their decision on the surgical indication for HT in PHP and to evaluate this situation not from an all-or-nothing point of view, but from a broader perspective based on whether HT is under control or not, or from a broader perspective based on the number of medications and whether it is under control with the current medications or not, or even whether it is under control or not despite the fact that one of the medications contains a potassium-sparing diuretic. However, this issue is still unclear and additional studies are needed in this field.

Another result obtained from this study was that the frequency of CAD was increased in patients with both mild and severe PHP. Factors such as increased blood pressure in PHP,[16] endothelial dysfunction,[23] hyperactivity in aldosterone-renin-angiotensin system,[5,6,18,19] insulin resistance and deterioration in metabolic parameters[22] may be considered as the reason for this increase. There are many studies showing an increase in total mortality and CAD in PHP.[24-26] Current guidelines do not indicate the presence of CAD in PHP as an indication for surgery for the time being,[2] again citing the lack of a decrease in CAD-related mortality after surgery in PHP and the fact that CAD-related mortality may increase in some patients after surgery.[24] On the other hand, a decrease in blood pressure,[17] improvement in endothelial dysfunction[23] and insulin resistance,[22] hyperactivity in aldosterone-renin-angiotensin system,[18] and CAD-related mortality[24] are observed after surgery in PHP. Although an association between CAD and mortality has been found in PHP, there are still unanswered questions, one of which is whether there is an increase in asymptomatic patients, and the other is whether it is hypercalcaemia or hyperparathyroidism that causes this. Lundgren et al.[27] found a relationship between increased calcium levels and CAD and mortality in a 20-year follow-up. In another study, it was observed that patients with chronic renal failure (CRF) and normal Ca levels but secondary hyperparathyroidism (SHP) had a higher rate of non-dipping pattern compared to patients with normal PTH levels.[28] In the study by Wang et al.[29] among patients with CRF and SHP on haemodialysis programme, improvement in blood pressure was observed in those who underwent parathyroidectomy, whereas an increase in diastolic blood pressure was observed in those treated with cinecalcet. As can be seen, the situation is intertwined and complicated. In present study, an association was found between Ca levels and CAD, but no association was found between CAD and HT and PTH. Randomised controlled studies are needed to clarify this issue.

Our study has some limitations; firstly, there may be deficiencies in the collection of some data due to its retrospective design, for example; smoking status, post-operative hypertension status, patients family history of CAD and and physical activity of patients. Secondly, mortality data could not be obtained in our study and therefore the effect of mild hypercalcaemia on mortality could not be evaluated. Thirdly, data on the number of anti-hypertensive drugs used could not be obtained.

CONCLUSION

Increased calcium levels in PHP are associated with HT regardless of the amount of increase, and increased Ca levels have an age-independent effect on the presence of CAD disease. No independent association was found between PTH levels and either HT or CAD. In this case, the answer to the question of whether PTH or increased Ca levels are responsible for cardiovascular events in PHP seems to be in favour of increased Ca levels. However, this issue needs to be supported by additional studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bursa City Hospital Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-5/12).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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